Accepted Manuscript

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PII: S1876-3820(18)30213-0
DOI: https://doi.org/10.1016/j.eujim.2018.05.003
Reference: EUJIM 794

To appear in:

Received date: 18-2-2018
Revised date: 13-5-2018
Accepted date: 13-5-2018

Please cite this article as: Xing Lan-Feng, Wu Yan, He Yi-Jing, Wang Fang-Fang, Zhu Yu-Hang, Ma Chun-Mei, Yan Yu-Ying, Sun Sai-Jun, Pan Jie-Xue, Robinson Nicola, Hardiman Paul J, Qu Fan.Transcutaneous electrical acupoint stimulation alleviates the anxiety levels of IVF: a prospective, randomized and controlled study.*European Journal of Integrative Medicine* https://doi.org/10.1016/j.eujim.2018.05.003

Transcutaneous electrical acupoint stimulation alleviates the anxiety levels of IVF: a prospective, randomized and controlled study

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Abstract

Introduction: It is recognized that all over the world, infertile women undergoing in vitro fertilization (IVF) experience high levels of stress, but most remain undiagnosed and untreated. This study explored whether transcutaneous electrical acupoint stimulation (TEAS) could relieve anxiety levels in infertile women.

Methods: A total of 360 infertile women with tubal blockage were randomized into four groups: control group, TEAS-2Hz group, TEAS-100Hz group and TEAS-2/100Hz group. After excluding patients who did not complete embryo transfer, 84, 84, 80 and 86 cases remained in the above groups respectively. Anxiety levels were measured using the Spielberger's State Trait Anxiety Inventory (STAI) and the Amsterdam Preoperative Anxiety and Information Scale (APAIS).

Results: We found that 2/100Hz TEAS treatment significantly decreased the levels of state anxiety and preoperative anxiety ($P<0.05$). In addition, there were indications that a100 Hz TEAS treatment could decrease the scores of APAIS.

Conclusions: TEAS using a frequency of 2/100Hz could help to alleviate state anxiety and preoperative anxiety levels.

The trial was registered at Chinese Clinical Trial Register (ChiCTR) with the identifier ChiCTR-TRC-14004493.

Keywords: Transcutaneous electrical acupoint stimulation (TEAS); in vitro fertilization (IVF); anxiety; randomized controlled trial (RCT).[1]

APAIS: Amsterdam Preoperative Anxiety and Information Scale; ART: Assisted reproductive technology; COH: Controlled ovarian hyperstimulation; CONSORT: Consolidated Standards of Reporting Trials; CPR: Clinical pregnancy rate; ET: Embryo transfer; IR: Implantation rate; ICSI: Intra-cytoplasmic sperm injection; IVF: In vitro fertilization; LBR: Live birth rate; NPY: Neuropeptide Y; STAI: Spielberger's State Trait Anxiety Inventory; STRICTA: Standards for Reporting Interventions in Clinical Trials of Acupuncture; TEAS: Transcutaneous electrical acupoint stimulation; TVOR: Trans-vaginal oocyte retrieval.

Introduction

In vitro fertilization (IVF), as an important assisted reproductive technology (ART), is chosen by more and more infertile couples, and is linked to over 400,000 babies born worldwide each year [1]. The treatment of IVF is usually stressful for infertile women and the emotional experiences of the IVF patients have drawn more and more attention in recent years [2]. Based on the Spielberger's State Trait Anxiety Inventory (STAI), anxiety levels in infertile women were significantly elevated during the IVF cycle [3]. Psychiatric disorders have been found in 30.8% of infertile women and 10.2% of men undergoing IVF treatment, and mood disorder is present in 26.2% of females and 9.2% of males, indicating that the psychiatric and mood disorders are common in both women and men undergoing IVF treatment [4]. In China, 23.2% of infertile women undergoing IVF or intra-cytoplasmic sperm injection (ICSI) had anxiety disorders [5]. However, the majority of the infertile couples with the psychiatric or mood disorder were undiagnosed and untreated [4]. A meta-analysis found there was a negative correlation between stress distress and pregnancy outcomes with ART [6]. The increased depression and anxiety scores of women during IVF treatment have notably been correlated with the lower number of oocytes and the women with higher state anxiety or depression scores on the day of trans-vaginal oocyte retrieval (TVOR) had significantly lower pregnancy rates [7]. Consequently, it is necessary to provide effective and safe treatment to decrease the anxiety levels of infertile women undergoing IVF and to improve their quality of life [8].

Transcutaneous electrical acupoint stimulation (TEAS), as a new and non-invasive acupuncture treatment, avoids the discomfort, bleeding or pain induced by the skin needling in the traditional acupuncture treatment and increases the reproducibility of acupuncture-like stimulation [9, 10]. TEAS has significant advantages

in alleviating mood disorders [11, 12]. TEAS has also shown to be a safe, easy and noninvasive technique for nursing home staff to improve depressive mood in old people [11]. The combination of acupressure and TEAS has been found to also significantly reduce the depressed mood and improve the sleep quality in hemodialysis patients [12]. The aim of the study was to see whether TEAS could also relieve anxiety levels of infertile women during the period from TVOR to embryo transfer (ET) in IVF treatment.

Methods

Subjects

In a six-month period (April 21, 2014 to October, 20, 2014), 486 infertile women with tubal blockage referred to Reproductive Medicine Center of Zhejiang Province, China (Department of Reproductive Endocrinology, Women's Hospital, School of Medicine, Zhejiang University, China) for IVF were screened. Among the patients screened, 121 women did not meet the inclusion criteria, and 5 women declined to participate. Finally, 360 infertile women with tubal blockage were included in the study. The long protocol for controlled ovarian hyperstimulation (COH) was used as previously described [13]. The subjects were randomized into one of four groups: a control group, a TEAS-2Hz group, a TEAS-100Hz group or a TEAS-2/100Hz group using a randomization chart constructed in Microsoft Excel with a proportion of 1:1:1:1. The random allocation sequence was concealed until the interventions were assigned. A nurse enrolled the participants and assigned them to their groups. The IVF clinicians and laboratory staff were blinded to the group assignment. The ET treatment was conducted three days after TVOR. In the statistical analysis, 6, 6, 10 and 4 cases respectively in the control group, TEAS-2Hz group, TEAS-100Hz group and TEAS-2/100Hz group were excluded, as these patients did not complete ET (Fig. 1).

Ethical permission to conduct the study was obtained from the Institutional Review Board of Reproductive Medicine, Women's Hospital, School of Medicine, Zhejiang University. The aim and methodology of the study were explained to the patients in detail. Voluntary participation was requested and informed consent was obtained from all of the participants. The subjects included in the study were infertile women with tubal blockage who were referred to the department for IVF. They were otherwise healthy women with regular menstrual cycles and normal sex hormone levels, and no other existing pelvic pathology. No structural abnormalities of the uterus or ovaries were found by vaginal ultrasound or laparoscopy. None of the women had received salpingectomy or ART therapy previously. We excluded the patients with neurological, mood or psychiatric disorders, the patients who were taking any anxiolytics, the patients who were receiving acupressure or acupuncture therapy, the patients with a history of smoking or drinking, or the patients who were not fluent in Chinese. All the partners of the women had normal spermiograms and sperm morphology. The present study adheres to the Consolidated Standards of Reporting Trials (CONSORT) statement [14], and Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) [15, 16]. The TEAS treatments were performed by two registered acupuncturists who have worked in Traditional Chinese Medicine (TCM) department for more than 5 years. The TEAS protocol is developed based on the clinical experience of our hospital, the TCM literature and consultation with six experts in Chinese medicine. The TEAS devices (HANS-100B) used in the study were provided by Nanjing Jisheng Medical Technology Co., Ltd, Nanjing, China.

Group and administration

Control group: The patients only followed the routine procedure of IVF treatment and no TEAS.

TEAS-2Hz group: TEAS was firstly administered for 30 min, 24 h before TVOR, using a frequency of 2Hz at the acupoints: SP10 (Xuehai, bilateral), SP8 (Diji, bilateral), LR3 (Taichong, bilateral), and ST36 (Zusanli, bilateral). At 2h before ET, TEAS was administered for 30 min using a frequency of 2Hz at the following acupoints: EX-CA1(Zigong, bilateral), RN4 (Guanyuan), PC6 (Neiguan, bilateral) and RN12 (Zhongwan). TEAS was applied to the patients through self-adhesive surface electrodes. The standard electrodes affiliated to the TEAS device were applied to the denuded skin and the intensity was set strong enough to elicit visible muscle contraction.

TEAS-100Hz group: TEAS was administered for 30 min, respectively at 24 h before TVOR and 2h before ET, using a frequency of 100Hz. The acupoints used and the manipulation were exactly the same as the TEAS-2Hz group above.

TEAS-2/100Hz group: TEAS was administered for 30 min, respectively at 24 h before TVOR and 2h before ET, using a frequency of 2/100Hz. The acupoints used and the manipulation were exactly the same as the TEAS-2Hz group above.

Measurement of anxiety

The levels of state anxiety, preoperative anxiety (including anesthesia related anxiety and surgery related anxiety) and the need-for-information were evaluated respectively on the morning of one day before TVOR (before the first TEAS treatment, defined as time-point T1) and on the morning of the day of ET (after the second TEAS treatment, defined as time-point T2) by four independent trained nurses who were out of the research team. They were all blinded to the group assignment. The levels of state anxiety were measured with the Chinese version of STAI, which is characterized by high reliability and good construct validity [17-19]. STAI includes 20 short items measuring state anxiety which refers to transitory emotional arousal or situational

distress at a particular moment in time and the score of each item ranges from 1 to 4 and a higher score reflects a higher level of state anxiety [20]. The levels of preoperative anxiety and the need-for-information were measured with the Amsterdam Preoperative Anxiety and Information Scale (APAIS) and the score of each item ranges from 1 to 4 and higher scores reflect higher levels of preoperative anxiety and the need-for-information[19, 21-23].

Sample size and data analysis

Power Analysis and Sample Size (PASS 11.0) was used to calculate the sample size. Power analyses performed prior to the study showed we should include at least 78 participants per group (allowing for a 20% loss to follow-up) for 90% power and p = 0.05 to detect a clinically significant change (10-point) in anxiety between groups.

Data were analyzed using the Statistical Package for Social Sciences (SPSS 19.0 for Windows). One-way analysis of variance (ANOVA) was used to evaluate statistical significances of continuous data. Chi-square test was used to compare categorical data. For all the hypothesis tests, a significance level was set at $P<0.05$.

Results

The baseline characteristics

There were no significant differences among the control group, TEAS-2Hz group, TEAS-100Hz group and TEAS-2/100Hz group on all the baseline characteristics ($P>0.05$) (Table 1).

The levels of state anxiety, preoperative anxiety and need-for-information

No significant differences existed among the four groups on the levels of state anxiety, preoperative anxiety (including anesthesia related anxiety and surgery related anxiety) and need-for-information at T1. At T2, after TEAS treatment, the levels of state anxiety

and preoperative anxiety (including anesthesia related anxiety and surgery related anxiety) of the TEAS-2/100Hz group were significantly lower than those of the other three groups (P<0.05). The anesthesia related anxiety levels of the TEAS-100Hz group were significantly lower than those of the control and TEAS-2Hz groups (P<0.05). The levels of need-for-information in the TEAS-100Hz and TEAS-2/100Hz groups were significantly lower than the other groups (P<0.05) and there were no significant differences between the TEAS-100Hz and TEAS-2/100Hz groups (P>0.05) (Table 2 and Supplementary table 1).

Adverse result

No side-effects were reported in any of the patients during the research and during the follow-up period.

Discussion

In the present study, 360 infertile women with tubal blockage referred for IVF were investigated to explore whether TEAS could relieve their anxiety levels. Patients were divided as follows according to the dose of stimulation provided; TEAS-2 Hz group, TEAS-100 Hz group, TEAS-2/100 Hz group or no stimulation (the control group). Treatment using 2/100Hz TEAS treatment significantly decreased the levels of state anxiety and preoperative anxiety in patients. Meanwhile, 100 Hz TEAS treatment could decrease the levels of anesthesia related anxiety and need-for-information to some extent.

Previous study found that the state anxiety levels were closely correlated to both CPR and LBR of the IVF patients, which was partly mediated by the activities in the hypothalamus-pituitary-adrenal axis and sympathetic nervous system [24]. Neuroticism-related personality traits also exhibited significant correlations with depressive and/or anxiety symptoms in the infertile women undergoing IVF, which may have negatively affected the IVF outcomes [25]. It may be necessary to conduct a

psychiatric and psychological screening for the infertile women before the IVF treatment started and if needed, to perform the preventive psychiatric and psychological interventions [26]. A Eastern Body-Mind-Spirit intervention approach was found to effectively decrease the anxiety levels of the infertile women undergoing IVF treatment [27]. Fluoxetine is sometimes prescribed to the IVF women with high anxiety levels, which can effectively alleviate the anxiety levels of the patients, however, other selective serotonin reuptake inhibitors or higher fluoxetine doses are still needed to relieve the emotional distress without affecting IVF outcomes [28]. The first mind-body therapeutic program for alleviating the uncertainty and anxiety during the IVF treatment has shown direct meaning for clinical practice [29].

Acupuncture has been found to have the potential to help IVF patients alleviate psychological and emotional issues associated with IVF treatment [30-32]. The authors' group has also ever found that auricular acupressure could help to reduce anxiety levels associated with IVF and to improve the outcomes of IVF partly through increasing the levels of neuropeptide Y (NPY) in the follicular fluids [19]. In this study, we explored whether TEAS could alleviate the anxiety levels of IVF. Effective frequency for TEAS ranges from 2 Hz to 100 Hz, and stimulation with different frequencies may generate totally different biological effects [33]. Generally, 2 Hz is chosen as a representative for low frequency, 100 Hz for high frequency, and 2/100 Hz for alternate low and high frequencies. This study demonstrated that TEAS using a frequency of 2/100Hz could help to reduce the anxiety levels associated with IVF. TEAS with a frequency of 2/100 Hz was also found to improve the IVF outcomes in our prior work [34], which was in accordance with the above studies.

During the IVF treatment, for most of the infertile women with various sociodemographic and biomedical backgrounds, the stress levels in the TVOR and ET

stages were eminently higher than those of the baseline stage [35]. The patients presented the highest stress and anxiety levels shortly before TVOR, which might negatively influence the implantation phase [36, 37]. In order to explore the baseline levels of the patients before TVOR, we conducted the first psychological measurement on the morning of the last day before TVOR in the present study. According to the clinical and research experiences from the authors' group, the infertile women often present notable anxiety levels during the period from the last day before TVOR to the day of ET [19]. Consequently, we chose the morning of the day of ET to perform the second measurement, as in this time-point, the TEAS treatment has completed and the ET operation will start shortly.

We concluded that TEAS using a frequency of 2/100Hz could help to reduce the anxiety levels associated with IVF, which provides an alternative treatment to alleviate the anxiety levels of the infertile women undergoing IVF. However, the conclusion may be a little limited, due to small sample size, short research period, and lack of the investigation of the underlying mechanism. Larger randomized, multicentre, double-blinded and placebo-controlled trials are expected to be conducted in the near future and the underling mechanism may also be investigated.

Confllicts of interest

None.

Acknowledgements

This work was supported by the Zhejiang Traditional Chinese Medicine Foundation (No. 2017ZA091); and the Zhejiang Traditional Chinese Medicine Foundation (No. 2017ZQ020).

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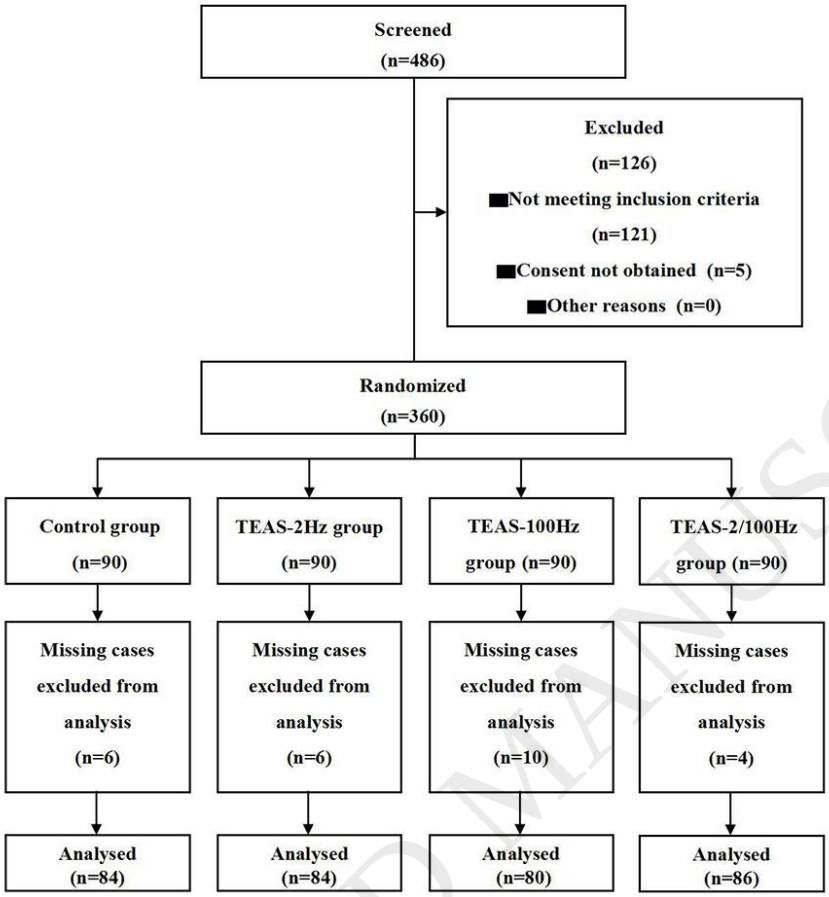
Figure Legends

Figure 1. The flow chart of the progress of participants through the trial.



Tables

Table 1. The baseline characteristics of the participants.

Items	Control group (n=84)	TEAS-2Hz group (n=84)	TEAS-100Hz group (n=80)	TEAS-2/100Hz group (n=86)
Ages (years)	31.24±4.91	30.83±4.57	32.18±4.77	31.99±4.56
BMI (kg/m^2)	22.17±5.99	23.11±4.61	21.98±4.90	22.21±4.19
Duration of infertility (year)	5.32±3.91	4.92±4.11	5.21±4.18	5.55±4.42
Day-3 LH	5.31±3.01	5.03±2.98	5.79±3.31	5.42±3.11
Day-3 FSH (nmol/L)	7.07±2.91	7.32±3.12	7.12±3.39	6.92±2.76
Day-3 TT(pmol/L)	1.41±0.10	1.50±0.09	1.59±0.12	1.39±0.08
Day-3 E2(pmol/L)	138.22±53.97	131.93±55.56	137.11±52.31	140.11±54.98
Cycle length (days)	36.11±8.72	35.54±8.12	37.91±9.02	34.13±8.26
rFSH administered (IU)	2365.21±711.22	2286.91±704.33	2231.14±742.39	2301.55±756.22
Induction length (days)	9.53±2.04	9.73±1.89	9.83±2.11	9.61±1.97
Number of oocytes	15.11±6.19	14.73±6.32	15.65±6.55	14.99±6.45
Number of follicles >14mm	12.87±5.09	11.98±4.87	12.98±4.91	12.49±5.11
Fertilization rate	902 / 1269 (71.08%)	905 / 1237 (73.16%)	884 / 1252 (70.61%)	918 / 1289 (71.22%)
Embryo cleavage rate	867 / 902 (96.12%)	881 / 905 (97.35%)	853 / 884 (96.49%)	894 / 918 (97.39%)
Good-quality embryo rate	629 / 902 (69.73%)	622 / 905 (68.73%)	594 / 884 (67.19%)	606 / 918 (66.01%)
Embryos transferred per cycle	1.96±0.62	2.04±0.71	2.16±0.66	2.11±0.62
Education level				
High	50 / 84 (59.52%)	45 / 84 (53.57%)	48 / 80 (60.00%)	54 / 86 (62.79%)
Medium	29 / 84 (34.52%)	33 / 84(39.29%)	27 / 80 (33.75%)	26 / 86 (30.23%)
Low	5 / 84 (5.96%)	6/ 84 (7.14%)	5 / 80 (6.25%)	6 / 86 (6.98%)
Living Area				
City	53 / 84 (63.09%)	55 / 84 (65.48%)	51 / 80 (63.75%)	50 / 86 (58.14%)
Urban	12/ 84 (14.29%)	13 / 84 (15.48%)	12 / 80 (15.00%)	15 / 86 (17.44%)
Country	19 / 84 (22.62%)	16 / 84 (19.04%)	17 / 80 (21.25%)	21 / 86 (24.42%)
Employment Type				
Full-time	37 / 84 (44.05%)	39 / 84 (46.43%)	36 / 80 (45.00%)	38 / 86 (44.19%)
Part-time	26 / 84 (30.95%)	23 / 84 (27.38%)	23 / 80 (28.75%)	25 / 86 (29.07%)
Non-employment	21 / 84 (25.00%)	22 / 84 (26.19%)	21 / 80 (26.25%)	23 / 86 (26.74%)

Note: Data were shown as mean ± S.D. *P<0.05, compared with the control group; $^{\#}P$<0.05 compared with the TEAS-2Hz group; $^{\$}P$<0.05 compared with the TEAS-100Hz group. TEAS: transcutaneous electrical acupoint stimulation; BMI: body mass index; Day-3: the 3rd day of spontaneous menstrual cycle; LH: luteinizing hormone; FSH: follicle stimulating hormone; TT: total testosterone; E2: estradiol; r-FSH: recombinant FSH.

Table 2. The levels of state anxiety, preoperative anxiety and need-for-information.

Items	Control group (n=84)	TEAS-2Hz group (n=84)	TEAS-100Hz group (n=80)	TEAS-2/100Hz group (n=86)
STAI (T1)				
State anxiety	44.31±9.55	42.88±8.97	44.55±9.19	43.76±8.52
APAIS (T1)				
Anesthesia related anxiety	3.28±1.31	3.41±1.45	3.32±1.52	3.49±1.57
Surgery related anxiety	4.05±1.47	4.12±1.39	4.21±1.42	3.87±1.20
Need-for- information	5.43±1.32	5.32±1.28	5.16±1.26	5.37±1.41
STAI (T2)				
State anxiety	39.27±11.62	41.82±11.44	38.14±10.01	28.97±8.13 * $^{\#\$}$
APAIS (T2)				
Anesthesia related anxiety	3.02±0.94	3.12±1.12	2.37±0.93 * $^{\#}$	1.76±0.61 * $^{\#\$}$
Surgery related anxiety	3.41±1.33	3.32±1.19	3.47±1.28	2.32±0.94 * $^{\#\$}$
Need-for- information	4.88±1.73	4.73±1.56	3.15±1.67 * $^{\#}$	2.93±1.85* $^{\#}$

Note: Data were shown as mean ± S.D. *P<0.05, compared with the control group; $^{\#}P$<0.05 compared with the TEAS-2Hz group; $^{\$}P$<0.05 compared with the TEAS-100Hz group. TEAS: transcutaneous electrical acupoint stimulation; T1: the time-point on the morning of the last day of trans-vaginal oocyte retrieval (before the first TEAS treatment); T2: the time-point on the morning of the day of embryo transfer (after the second TEAS treatment); STAI: state trait anxiety inventory; APAIS: Amsterdam preoperative anxiety and information scale.